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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/674,666	09/29/2003	Mike Clark	PHOE0001-100	5283

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EXAMINER	
LE, EMILY M	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/674,666	CLARK, MIKE	
	Examiner	Art Unit	
	Emily Le	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 February 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-19,22,25,41,42 and 52-73* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-19,22,25,41,42 and 52-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims Status

1. Claims 20-21, 23-24, 26-40 and 43-51 are cancelled. Claims 52-73 are added. Claims 1-19, 22, 25, 41-42 and 52-73 are pending and under examination.

Claim Rejections - 35 USC § 112

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

3. Claims 3, 52 and 54 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims are indefinite for the recitation "conventional antiviral compounds". It is unclear what is intended by Applicant for the term "conventional". Is the term "conventional", when added before "antiviral compounds" intended to add a special limitation?

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-19, 22, 25, 41-42 and 52-73 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting or reducing HCV 1b replication in an individual infected with HCV, and i) having hepatocellular carcinoma or ii) cells that do not express arigininosuccinate synthase (ASS) and are auxotrophic for arginine by administering an effective amount of a composition comprising arginine deiminase bonded with polyethylene glycol. The

specification does not reasonably provide enablement for a method of inhibiting or reducing HCV replication in an individual infected with HCV, in the absence of hepatocellular carcinoma, or cells that do not express arigininosuccinate synthase (ASS) and are auxotrophic for arginine by administering an effective amount of a composition comprising arginine deiminase bonded with polyethylene glycol. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

As presented, the claims are broadly directed toward a method of inhibiting or reducing the replication of all hepatitis C viral serotypes in an individual with the administration of a composition that comprises arginine deiminase bonded with polyethylene glycol. However, it is noted that the disclosure teaches a method of inhibiting or reducing the replication of hepatitis C viral serotype 1b in an individual that is infected with HCV serotype 1b and i) having hepatocellular carcinoma or ii) cells that do not express arigininosuccinate synthase (ASS) and are auxotrophic for arginine with the administration of a composition that comprises arginine deiminase bonded with polyethylene glycol. Appropriately drafted claim language directed toward the indicated enabled embodiment would be acceptable.

In a telephonic conversation with Gwilym J. O. Attwell, during the week(s) of 04/04/05-04/11/2005, the Examiner clearly indicated that the claimed method would be allowable upon amending the claims to require the individual to have hepatocellular carcinoma or cells that do not express arigininosuccinate synthase (ASS). However, Applicant's representative failed to accept the proposed amendment.

To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. In Genentech *Inc. v. Novo Nordisk* 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); *In re Wright* 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also *Amgen Inc. v. Chugai Pharm. Co.,* 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); *In re Fisher* 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in *In re Wands* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in *Ex parte Forman* [230 USPQ 546, 547 (Bd Pat App Int 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

In the instant, Applicant is clearly not enabled for all genotypes of HCV, as demonstrated by Table 3, provided in the specification. Table 3 summarizes that arginine deiminase bonded to polyethylene glycol is **not effective** in inhibiting or reducing HCV, serotype 2c, in individuals infected with HCV, serotype 2c, and diagnosed with hepatocellular cancer. Ergo, in light of the data presented, the claimed invention is not found to be enabling for all HCV genotypes.

Furthermore, it is readily apparent from the specification that the effectiveness of arginine deiminase bonded to polyethylene glycol to inhibit or reduce HCV, serotype 1b, replication is dependent upon the presence of hepatocellular carcinoma cells, which possess following properties: do not express arigininosuccinate synthase (ASS) and are auxotrophic for arginine, as exemplified by Applicant's disclosure. The disclosure speculates that the mechanism of action for arginine deiminase bonded to polyethylene glycol against viral replication is by lowering extracellular arginine, which thereby inhibits nitric oxide synthesis.

In the instant, the lowering of arginine and inhibition of nitric oxide synthesis are dependent on ASS. ASS is the necessary catalyst for synthesis of arginine and nitric oxide from citrulline. In the absence of ASS, the presence of arginine and nitric oxide is limited. This limitation can also be further enhanced with the introduction of arginine deiminase. Arginine deiminase is the necessary catalyst for the degradation and conversion of arginine to citrulline. Thus, by severing arginine and nitric oxide synthesis with the dual action offered by arginine deiminase and the absence of the essential ASS enzyme, the hepatocellular carcinoma cells are killed—as exemplified by Izzo et al. Izzo et al. teaches that arginine deiminase kills hepatocellular carcinoma cell lines in vivo and in vitro [1]. The reduction in hepatocellular carcinoma cells leads to an inhibition or reduction on HCV replication, wherein hepatocellular cells is the primary site for HCV replication[2]. Thus, it is gathered that Applicant's observation of inhibition or reduction of HCV, serotype 1b is the result of killing hepatocellular carcinoma cells with arginine.

[1] Izzo et al. Pegylated arginine deiminase treatment of patients with unresectable hepatocellular carcinoma: results from Phase I/II studies. Journal of Clinical Oncology. 05/2004, Vol. 22, No. 10, pp. 1815-1822.
[2] Fields et al. Fields Virology. Lippincott Williams & Wilkins, 4th Edition, 2001, Vol. 1,1137.

deiminase bonded with polyethylene glycol. The killing of hepatocellular carcinoma cells with arginine deiminase bonded with polyethylene glycol causes a chain reaction that results in the inhibition or reduction of HCV, serotype 1b.

Ergo, in view of the analysis provided above, which compared and contrasted the claimed invention with the disclosure that is provided in the specification, the specification is not found to be enabling for the full scope of the claimed invention.

Moreover, the art also recognizes that antiviral development is not a trivial undertaking. Antiviral development frequently requires in vitro, in vivo, and preliminary clinical studies to truly ascertain the efficacy of any given antiviral compound, as evidenced by Oberg et al.[3] Oberg et al. teaches several antiviral drug screening processes, wherein each process is directed at a specific category of viruses. The general outline of each process includes in vitro studies, in vivo animal studies, safety evaluations and clinical trials. Oberg et al. also notes that the validity of different animal models can only be determined by evaluation of antiviral activity in patients. The teaching of Oberg et al. is also exemplified by Yarchoan et al.[4] Yarchoan et al. teaches that in vitro antiviral activity does not correlate with in vivo antiviral activity. Ergo, in the instant art, it is clear that in vitro data does not necessarily correlate with in vivo data and/or clinical observation. Furthermore, it is also well known in the art that the inhibitory activity of an antiviral agent against a particular virus cannot be equated with its inhibitory effect against another virus.[5]

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[3] Oberg et al. Screening for new agents. Eur. J. Clin. Microbiol. Infect Dis., July 1990, Vol. 9, No. 7, p. 466-471.
[4] Yarchoan et al. Correlations between the in vitro and in vivo activity of anti-HIV agents: implications for future drug development. J. Enzyme Inhibition. 1992, Vol. 6, pp. 99-111.
[5] Wiltink et al. Antiviral drugs. Pharmaceutisch Weekblad Scientific edition. 1991, Vol. 13, No. 2, pp. 58-69.

More specifically, the development of HCV antiviral drugs is limited by the absence of a stable cell-based system to support HCV replication and the paucity of effective animal models, as noted by Dev et al.[6] Dev et al. also summarizes the challenges that faces the development of an effective HCV antiviral drug, this includes: i) high genetic diversity and geographic distribution of HCV genotypes, antiviral agents must be effective against different genotypes; ii) the high rate of mutational change with in the HCV genome, which underscores the importance of drug resistance; and the lack of reliable, reproducible and efficient HCV cell culture systems and small animal models.

Ergo, in view of the analysis provided above, which discusses the challenges that accompanies the instant art and the limited teaching that is provided in the specification—which does not commensurate in full scope with the claimed invention and does not teach the skilled artisan how to overcome the challenges that is noted in the art for HCV antiviral; the claims are rejected under 35 U.S.C. 112, first paragraph because the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F. 2d 1557, 1562, 27 USPQ 2d 1510, 1513 (Fed. Cir. 1993).

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[6] Dev et al. Antiviral Therapy: Future Treatment of Hepatitis C: What's around the Corner. Infect. Med. 2001, Vol. 21,

Conclusion

6. No claim is allowed.

7. Allowable subject matter: a method of inhibiting or reducing the replication of hepatitis C viral serotype 1b in an individual that is infected with HCV serotype 1b, and i) having hepatocellular carcinoma or ii) cells that do not express arigininosuccinate synthase (ASS) and are auxotrophic for arginine with the administration of a composition that comprises arginine deiminase bonded with polyethylene glycol.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Emily Le whose telephone number is (571) 272 0903. The examiner can normally be reached on Monday - Friday, 8 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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